European Review for Medical and Pharmacological Sciences 2022; 26: 7474-7481

Pulmonary hypertension in the elderly. Is it an overdiagnosis or a distinct entity?

N. ÖCAL, M. ÇELIK, N.K. SATIŞ

Department of Pulmonology, Gulhane Medical Faculty, Health Sciences University, Ankara, Turkey

Abstract. – OBJECTIVE: The diagnosis of pulmonary hypertension (PH) in the elderly has become more common, recently. The possibility of overdiagnosis or misdiagnosis may arise in the elderly due to accompanying physiological changes and comorbidities. In this study, we aimed at revealing the clinical findings of individuals aged 60 years and older who were diagnosed with Group 1 and Group 4 PH, and at determining their differences with younger adults.

PATIENTS AND METHODS: Patients aged 60 years and older who were diagnosed with PH were identified. Among these patients, patients with a diagnosis of Group 1 PH (PAH) and Group 4 PH (CTEPH) were selected. A control group was formed from young and middle-aged patients. Demographic, clinical and hemadynamic characteristics of the elderly patients and the control group were analyzed.

RESULTS: The mean WHO Functional Class and the Charlson Comorbidity Index score were significantly higher; the mean EF was significantly lower in the elderly. The right heart catheterization results were assessed. While the mean PAP was significantly higher in young-middle-aged patients (49.6 *vs.* 39.2 mmHg) (*p*=0.03), the mean PCWB was significantly higher in the elderly (11.4 *vs.* 8.1 mmHg) (*p*=0.005). The young-middle-aged patients had a significantly higher mean PVR values (10.7 *vs.* 8.3 WU) (*p*=0.01).

CONCLUSIONS: Comorbidities and age-related functional losses may complicate the diagnosis of PH in elderly. Group 2 PH, which we frequently encounter in the elderly, may mask the true Group 1 or Group 4 PH in these patients. PH should be kept in mind in the elderly patients with unexplained exertional dyspnea.

Key Words:
Pulmonary hypertension, Elderly, Geriatric, Pulmonary artery, CTEPH.

Introduction

Pulmonary hypertension (PH) is a disease characterized by progressive increases in the pulmonary artery pressure (PAP) and the pulmonary vascular resistance (PVR) and can be fatal with right ventricular failure. The disease consists of five main groups, and the most common forms are Group 2 (PH associated with left heart diseases) and Group 3 (PH associated with chronic lung diseases and hypoxemia). If we separate Group 5 PH as "multifactorial/unclear PH associated with underlying chronic diseases", the main patients who are privileged in the diagnosis and treatment approaches of physicians dealing with PH are mostly in Group 1 PH [Pulmonary arterial hypertension (PAH)] and Group 4 PH [Chronic thromboembolic PH (CTEPH)] groups. The diagnostic algorithms and treatment approaches of the patients in these two groups are specialized and are carried out by centers experienced in this field [1-3]. It is also very difficult to generate demographic and epidemiological data, as PH patients consist of different subgroups. Therefore, the best approach is to evaluate the subgroups under different headings.

Pulmonary arterial hypertension (PAH) is a disease known to generally affect women of childbearing age. However, PAH is increasingly being diagnosed in the elderly population. The diagnosis of PAH may be delayed due to the reductions in exercise capacity, which we frequently encounter due to comorbidities such as coronary artery disease and heart failure, which naturally have a high incidence and prevalence in the elderly population. However, in recent years, this patient group is being diagnosed more and more with the increase in awareness on this issue, the spread of tests and the development of perception towards PAH in the whole medical world with the contribution of new treatment modalities. Physicians include PH more in the differential diagnosis in the etiological evaluation of exertional dyspnea, which they cannot explain with current clinical findings[2,4].

Advanced age, which is one of the pulmonary embolism risk factors, causes chronic thromboembolic PH (CTEPH) to be seen more frequently in elderly patients. This increases the possibil-

Corresponding Author: Nesrin Öcal, MD; e-mail: nesrinbaygin@yahoo.com

ity of CTEPH in the elderly and, therefore, the awareness of physicians. As a result, the diagnosis of CTEPH is made more frequently and more easily in the elderly. In the light of real-life data from all over the world, the mean age at diagnosis of CTEPH is approximately 63 years, and unlike PAH, there is no female predominance. On the other hand, in patients without a previous history of acute pulmonary thromboembolism, this diagnosis can easily be overlooked, just like PAH [1,5]. In addition to the increase in comorbidities with advancing age, some physiological changes that occur with age also complicate the diagnosis. Weakening of respiratory muscle strength and decrease in exercise capacity with advancing age reduces effort capacity. Its effect on the pulmonary circulation is considered physiological up to a certain limit. A 1 mmHg/deca increase in systolic PAP (sPAP) is considered within physiological limits[6].

Considering all these conditions, it is obvious that elderly patients should be evaluated from a different perspective in terms of PH. However, data and studies on this subject offer very limited information. For this reason, it will be instructive to examine the characteristics of elderly patients in detail based on real-life data. This study aimed to reveal the clinical findings of individuals aged 60 and over who were diagnosed with Group 1 and Group 4 PH and their differences from the younger adults.

Patients and Methods

We obtained approval from the Local Ethic Committee. The files of patients diagnosed with PH between January 1, 2017, and December 31, 2021 were reviewed retrospectively.

Study Design

Patients aged 60 years and older who were diagnosed with PH were identified. Among these patients, patients with a diagnosis of PAH and CTEPH were selected. Those who had clinical, laboratory and radiological data were included in the study. Patients whose echocardiography (ECHO) and right heart catheter (RHC) results could not be reached were excluded from the study. Patients whose hemodynamic measurements were made in another center or diagnosed in a different hospital were also not included in the study.

All patients were diagnosed in the light of the diagnostic algorithms of the current ERS/ESC guideline. CTEPH was radiologically excluded for the diagnosis of group 1 PH, even in patients without an index history of pulmonary embolism. All of the patients were diagnosed with PH by RHC under fluoroscopy in our hemodynamics laboratory. All RHCs were made by the same cardiologist and his team who are very experienced in this field. Vasoreactivity test was also applied to the patients within the indications.

Demographic characteristics of the patients, PH groups, ECHO findings, RHC findings, World Health Organization (WHO) functional classes (FC), 6-minute walk test (6MWT) distances and Charlson comorbidity index (CCI) scores were recorded. We calculated and recorded the CCIs of the patients from their medical records. Based on the CCI scores of the patients, the severity of comorbidity was categorized into three grades: mild (CCI scores of 1–2), moderate (CCI scores of 3–4) and severe (CCI scores ≥5). In order to reveal whether the characteristics of elderly patients differ from those of non-elderly patients, a control group was formed from young and middle-aged patients, meeting the same inclusion criteria and having the same number as the study group. In order to achieve objectivity in the mean age, young and middle-aged patients with appropriate data were ranked according to age, and cases were selected by skipping at certain intervals.

Statistical Analysis

The data of the study group patients were analyzed within themselves. Afterwards, the study and control groups were compared statistically and evaluated. The mean and standard deviation (± SD) were calculated for continuous variables and proportions were calculated for categorical variables. Chi-square and Fisher exact tests were used in univariate analysis of categorical variables; and Student-T and Wilcoxon rank-sum tests were used in univariate analyzes of continuous variables. Tests were selected according to their usefulness to meet assumptions for binary comparisons. A p-value < 0.05 was considered statistically significant.

Results

In a 5-year period, a total of 104 patients aged 60 years and over were diagnosed with Group 1 (n=62) and Group 4 (n=42) PH. Of these, 62 patients (31 patients with PAH, 31 patients with CTEPH) with appropriate data were randomly selected and data of these patients were compiled. In order to obtain a control group against elder-

Table I. Comparison of the demographic and clinical characteristics of geriatric patients with PAH and CTEPH and the control group at the time of diagnosis.

		Geriatric group (n= 62)	Control group (n= 62)	*p*
Age (years)		72.63 (± 6.76)	46.67 (± 12.68)	-
Gender	**Female (F)**	48 (77.42%)	41 (66.13%)	-
	Male (M)	14 (22.58%)	21 (33.87%)	
Group 1 PH (PAH)		31 (29 F, 2 M)	31 (22 F, 9 M)	**0.05**
Group 4 PH (CTEPH)		31 (18 F, 13 M)	31 (19 F, 12 M)	
FC		3.3 ± 0.6	2.5 ± 0.5	**0.01**
6DMWT (m)		307.5 ± 43.5	412.2 ± 63.4	**0.04**
Charlson comorbidity index score		3.6 ± 0.8	1.3 ± 0.4	**0.01**

F: female, M: male, PH: Pulmonary hypertension, PAH: Pulmonary arterial ypertension, CTEPH: chronic thromboembolic pulmonary hypertension, FC: functional class, 6MWT: 6 minutes walk test.

ly patients diagnosed with PAH and CTEPH, 62 cases (31 patients with PAH, 31 patients with CTEPH) were selected by randomization among our adult patients under the age of 60 who had been diagnosed with PH in the last 5 years. In the control group, young and middle-aged patients were ranked according to age in order to achieve objectivity in the mean age and to ensure that the mean age could reflect the whole group, and cases were selected by skipping at certain intervals.

Demographic Findings

Study group (elderly patients)

The mean age of the patients was 72.63 (±6.76) years. In the elderly group, 48 (77.42%) of the cases were female and 14 (22.58%) were male. Among 31 patients with Group 1 PH (PAH), 6 cases (19.35% of PAH patients) were diagnosed with PAH associated with connective tissue disease and 24 cases (77.42% of PAH patients) with idiopathic PAH (iPAH). When PH groups were compared according to genders, all but 2 of the male patients were diagnosed with CTEPH (86.6%), while 61.7% of the female patients were diagnosed with PAH. Although the number of female cases was high in total, the gender distribution difference was especially more pronounced in patients with PAH. The distribution of PAH and CTEPH patients differed significantly between gender groups ($p<0.05$) (Table I).

Control group (young-middle-aged patients)

The data of young-middle-aged patients with PAH (n=31) and CTEPH (n=31) were analyzed. The ages of the patients ranged from 18 to 59 years. The mean age of the patients in the control group was 46.67 (±12.68) years. Gender distribution in the control group was similar to that of the elderly patients. Although the total number of female cases was high also in young-middle-aged patients, as in the elderly, the difference in gender distribution was not as evident as in the elderly. But still, the distribution of PAH and CTEPH patients differed significantly between gender subgroups of young-middle-aged patients ($p<0.05$) (Table I).

Clinical Findings

The WHO FCs of patients were obtained from clinical histories or records in their files. While the mean of the WHO FCs was 3.3±0.6 in elderly patients, it was 2.5±0.5 in young-middle-aged patients. The mean WHO FC was significantly higher in the elderly ($p=0.01$). The mean 6MWT distance was higher in control group. The difference between the results of 6MWT of the groups was also statistically significant ($p=0.04$). We used CCI to estimate the comorbidity burden in patients. When the mean CCI scores were compared, it was found that the score was significantly higher in the elderly ($p=0.01$) (Table I).

Hemodynamic findings: The initial ECHO and RHC findings of the patients during the diagnosis period were examined.

- *ECHO findings:* We observed that the mean sPAP was significant lower in elderly patients than in young-middle-aged patients ($p=0.05$). The Ejection fraction (EF%) of the patients was also analyzed. The EF% in the elderly was 53.6±4.5, and it was significantly lower than the young-middle-aged patients who had a mean EF of 75.9±5.7 ($p=0.01$). The mean tricuspid regurgitation velocity (TRV) and the right atrial area (RAA) were also lower in the elderly, but the

Table II. Comparison of echocardiography and right heart catheterization findings at the time of diagnosis between geriatric patients and the control group.

	Geriatric group (n= 62)	Control group (n= 62)	*P*
sPAB (mmHg)	72.2 ± 12.7	83.9 ± 13.6	**0.05**
EF (%)	53.6 ± 4.5	75.9 ± 5.7	**0.01**
TRV (m/s)	2.8	3.1	0.55
RAA (mm^2)	25.8 ± 4.4	27.2 ± 5.1	0.65
mean PAP (mmHg)	39.2 ± 6.4	49.6 ± 9.3	**0.03**
PCWP (mmHg)	11.4 ± 1.7	8.1 ± 1.5	**0.005**
PVR (WU)	8.3 ± 2.6	10.7 ± 2.8	**0.01**

sPAB: systolic pulmonary arterial pressure, EF: ejection fraction, TRV: tricuspid regurcitation velocity, RAA: right atrial area, mean PAP: mean pulmonary arterial pressure, PCWP: *pulmonary capillary wedge pressure,* PVR: pulmonary vascular resistance.

difference was not significant in both parameters (p>0.05) (Table II).

- *RHC findings:* All RHC procedures were performed by the same cardiologist. The results were evaluated, and the mean data of the study group and control group were compared. The mean PAP was significantly higher in young-middle-aged patients (49.6±9.3 mmHg *vs.* 39.2±6.4 mmHg). The mean pulmonary capillary wedge pressure (PCWP) was significantly higher in the elderly (11.4±1.7 mmHg *vs*. 8.1±1.5 mmHg). When the mean PVR results were compared, it was observed that young-middle-aged patients had a significantly higher mean PVR (10.7±2.8 WU *vs.* 8.3±2.6 WU) (Table II and Figure 1).

Discussion

In this study, we wanted to draw attention to the difficulties and complexities in the diagnosis of PH in elderly. When the aging world population and newly developing diagnosis-treatment regulations come together, the diagnosis of PH to become more common in the elderly. Our results showed that both Group 1 and Group 4 PH have substantial incidences in the elderly. In addition, it is supported by our results that Group 2 PH, which we frequently encounter in the elderly, may mask the true Group 1 or Group 4 PH in these patients[7]. Infact, it is clear that a special title should be specified for PH in the elderly. In this respect, we think that our study results will contribute to clinical practice.

The effects of aging on the respiratory system are well known. A progressive decline in lung function with normal aging is often considered to be within physiological limits. This condition is associated with changes in the mechanics of the lung-thorax system, resulting in an increase in the chest wall stiffness, a decrease in the static elastic recoil of the lung, and a decrease in the respiratory muscle strength. On the other hand, the loss of total pulmonary capillary volume of the lung by the age was also shown. All these factors may lead to a progressive increase in PVR with aging, which may predispose to the development of PH. Moreover, the fact that this condition is mostly assumed within physiological limits and attributed to old age, complicates the diagnosis of PH in the elderly. The cardiovascular system also shows significant changes with aging. Age-related vascular stiffness has been shown to contribute to isolated systemic systolic hypertension in the elderly. As expected, the pulmonary vascular bed also suffers from this situation. The decrease of the left heart compliance due to aging can lead to a progressive left ventricular diastolic dysfunction. As a result of both left heart failure and progressive increase in pulmonary artery stiffness, sPAP increases by approximately 1 mmHg per decade. As a result of all these changes, normal aging can lead to overdiagnosis of PH or an underestimation of PAH in the elderly population potentially. PAH may be suspected, especially if an elderly patient shows hemodynamic changes that are "out of proportion to age" with elevated PVR and mPAP[3,4,8-11].

In addition to the routine changes in the pulmonary and cardiovascular systems that occur with aging, the increase in the number and the severity of comorbidities complicates the situation in this age group. It is a fact that chronic diseases and comorbidities in elderly patients complicate the diagnosis and treatment approach of PH.

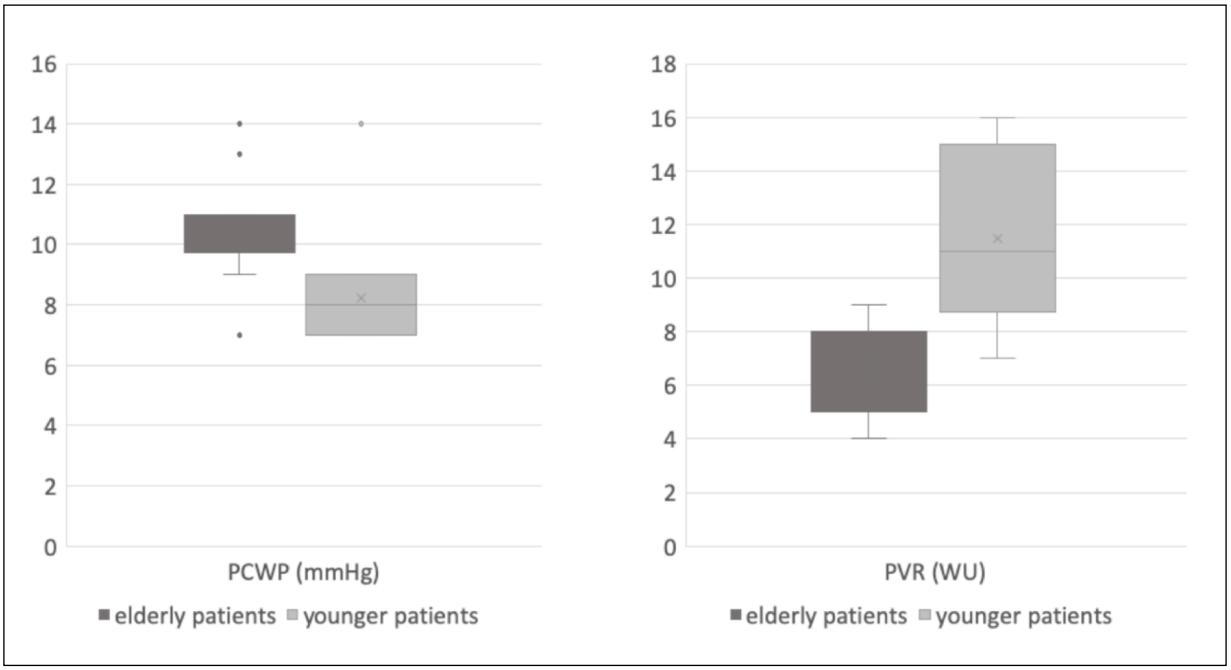

Figure 1. Distribution of PCWP and PVR values of elderly and younger patients. PCWP: pulmonary capillary wedge pressure, PVR: pulmonary vascular resistance.

Along with the physiological effects of age, comorbidities also mask the symptoms and signs of PH, leaving us with diagnostic problems. Thus, it seems reasonable to review and rate the presence of these comorbidities in elderly. Based on this idea, we wanted to estimate the comorbidity burden in these patients. For this purpose, we preferred to use CCI, which is an easy and useful scoring system, to predict the comorbidity burden. It was not surprising that the mean CCI score was higher in the elderly than in the younger. This reinforced the idea at the beginning of our study that the diagnosis of PH is more complex and difficult in the elderly. In this age group with intense comorbidities, both misdiagnosis and overdiagnosis of PH are very likely[12,13].

Despite all these complex relationships, the frequency of PH diagnosis in the elderly is increasing with the development of diagnostic methods, new treatment modalities and awareness of the PH. In fact, in studies conducted in recent years, it has been observed that the mean age at diagnosis of PAH patients is significantly higher than previous studies. After 1995, this increase became evident. Between 1990 and 2002, the frequency of PAH increased 3.4 times in patients over 65 years of age. The current registry studies demonstrated that there is an increase in the mean age of PAH diagnosis and the proportion of male patients. If both the US and European registries are considered together, it is seen that the rate of patients aged >70 years among patients with PAH is 9-13.5%; and the mean age at diagnosis is ~50 years. In a single-center registry, the mean age of diagnosis of idiopathic PAH was 55±16 years. In data published from the Swiss registry, the mean age at diagnosis of PAH was >60 years, with 56% of patients being female. A very striking demographic data came from another European registry and found the median age at diagnosis to be 71 years and reported that 63% of the cases were >65 years old. Given all this combined with an aging population worldwide and an increasing life expectancy, it means that it is no longer uncommon to see geriatric PAH patients[3,14-16].

Situations seem similar in CTEPH. In a retrospective study conducted in a PH center in the UK, the data of 411 CTEPH patients who underwent PEA were analyzed. They found that 25.06% of the patients who went to PEA were >70 years old. Gender distribution was found to be similar in both patients under the age of 70 and above. The 43.8% of young-middle-aged patients and the 51.5% of patients aged >70 years were female. The frequency of peripheral disease was significantly higher in elderly patients. The mean WHO FC was higher in the elderly in general, but the difference was not significant. While the mPAP

was found to be significantly lower in the elderly, no significant difference was found between the groups in terms of the mean PVR[17]. Berman et al[18] investigated the data of 411 patients, 103 of whom were aged ≥70 years, who underwent pulmonary endarterectomy (PEA). They observed that distal disease was more common in elderly patients, and the mean FC and 6MWT distances were worse than in younger patients. In light of the results, the researchers stated that PEA in patients aged ≥70 years was of acceptable safety. Advanced age should be considered when assessing eligibility for PEA, but age alone should not be a contraindication for surgery. In our results, similar to the literature, CTEPH was significantly common in the elderly. The true diagnosis of CTEPH, which has a curative treatment possibility contrary to PAH, gains more importance in the elderly.

The current hemodynamic definition of PAH (ie, an mPAP >20 mmHg and PCWP <15 mmHg) does not always clearly distinguish between pre- and post-capillary PH. Shapiro et al[19] examined 48 cases over 65 years of age with a probable diagnosis of iPAH and showed that the PCWP >15 mmHg in the 56%. In this case, the RHC findings did not fully meet the hemodynamic criteria for iPAH in these patients. Conditions suggestive of Group 2 PH (EF <50%, patients with significant mitral or aortic valve disease) were excluded in this study. However, the mean PCWP was higher than expected in most of the patients. It is well known that elderly individuals with PCWP>15 mmHg may have PH secondary to heart failure with preserved EF. However, Shapiro et al[9] suggested that PH with high PCWP may still be PAH and could be categorized as Group 1 PH despite not meeting the relevant hemodynamic criteria. They suggested that although PCWP increases with increased LV end-diastolic pressure (LVEDP), elevated LVEDP may be the result of chronic right ventricular (RV) overload caused by iPAH. There are also other results and ideas in the literature that support this situation[20,21]. In the younger age group, the effect of RV on left ventricular end-diastolic pressure (LVEDP) is modulated by the relative stiffness of the interventricular septum and LV free wall. In normal hearts, the interventricular septum is less rigid than the LV free wall. On the other hand, in iPAH, the septum is stiffer than the LV free wall due to chronic RV pressure overload. Therefore, the effect of RV on LVEDP is weaker than in normal hearts. This allows us to see a normal PCWP in most patients with iPAH. However, in elderly patients, vascular, LV systolic, and LV diastolic stiffness increase with the age. Therefore, elderly patients may have isolated pulmonary arteriopathy with a PCWP>15 mmHg. The PAH, which is already difficult to diagnose in the elderly, becomes more complex and mysterious with such age-related changes. In our study, the mean PCWP was also observed to be higher in the elderly than in the younger patients (Figure 1). Such that, hemodynamic measurements of some patients whose PCWP measurements were at the border during RHC, were repeated after controlled diuretic treatment without dehydrating them[22].

The mysteries of pulmonary hemodynamics in elderly do not end there. In geriatric patients who have heart failure with preserved EF, the complicated situation we are talking about with PCWP may be reversed. In other words, the patient may present with a PCWP lower than expected due to advanced RV failure in patients with Group 2 PH. In such situation, fluid challenge during RHC and exercise tests will guide the differential diagnosis in elderly patients[23]. In the COMPERA registry, this situation also remained largely mysterious. In this registry, iPAH was noted as the most common cause of PH in elderly patients[16]. However, it is known that most centers participating in the COMPERA study do not routinely perform fluid loading during RHC. Therefore, it is conceivable that some patients with LV diastolic dysfunction may have been misclassified as iPAH. For these reasons, it is difficult to distinguish post- capillary from pre-capillary PH. It is important for clinicians to distinguish between these two subdiagnoses, because PAH-specific drugs may worsen LV function in patients with pre-capillary PH. It seems that the landscape is getting more complicated. Even all these data can be accepted as proof that PH in the elderly should be considered as a separate entity.

The confusion is not limited to these situations. An inverse relationship between age at diagnosis and the mPAP has been previously analyzed. In addition, the myocardial performance index of the RV was lower in elderly patients than in younger patients. This leads to better RV adaptation of the elderly to higher PAP. Therefore, mPAP values in the elderly can be expected to be lower than in the younger adults. Similarly, the PVR can be lower in the elderly. In the RHC data of our patients, the mean PVR was significantly lower in the elderly than in the younger patients. While the mean PVR was 8.8 WU in the elderly, it was 11.7 WU in the younger cases. As a result of all the paradoxical relationships,

it has been observed that survival is worse in elderly despite their better hemodynamic profiles[10,19].

Conclusions

According to the results of this study, CTEPH may be encountered more frequently, especially in male elderly. The comorbidities and the age-related functional losses may complicate the diagnosis. Considering that the mean sPAP values may be lower in elderly, it is necessary to be alert for PH in this age group. Due to the lower EF% and lower sPAP, the ECHO findings in elderly patients may lead to overlooked diagnosis of PH. It is necessary to be careful in the differential diagnosis during RHC applied in the elderly, even in cases of borderline PCWP or PVR. We emphasize that PH in the elderly is not as rare as previously described, and an individualized investigation of PH in the elderly will further improve this issue.

Conflicts of Interest

The authors declare no conflicts of interest.

Ethics Approval

The study was performed according to the principles of the Declaration of Helsinki and the protocol was approved by the Local Ethics Committee (Gülhane Scientific Research Ethics Committee decision; No: 2020/21, 2020-503).

Informed Consent

Informed consent was not required since the study was retrospective.

Authors' Contributions

All authors contributed to the study conception and design. Material preparation and data collection were performed by NÖ and MÇ. Data analysis was done by NÖ and NKS. The first draft of the manuscript was written by NÖ, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding

This study was not funded.

ORCID ID

Nesrin Öcal: 0000-0002-3789-7769
Murat Çelik: 0000-0002-7864-4952
Neslihan Kayahan Satış: 0000-0002-6802-7926

References

1) Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M; ESC Scientific Document Group. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J 2015; 46: 903-975.
2) Badesch DB, Raskob GE, Elliott CG, Krichman AM, Farber HW, Frost AE, Barst RJ, Benza RL, Liou TG, Turner M, Giles S, Feldkircher K, Miller DP, McGoon MD. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. Chest 2010; 137: 376-387.
3) Ling Y, Johnson MK, Kiely DG, Condliffe R, Elliot CA, Gibbs JS, Howard LS, Pepke-Zaba J, Sheares KK, Corris PA, Fisher AJ, Lordan JL, Gaine S, Coghlan JG, Wort SJ, Gatzoulis MA, Peacock AJ. Changing demographics, epidemiology, and survival of incident pulmonary arterial hypertension: results from the pulmonary hypertension registry of the United Kingdom and Ireland. Am J Respir Crit Care Med 2012; 186: 790-796.
4) Berra G, Noble S, Soccal PM, Beghetti M, Lador F. Pulmonary hypertension in the elderly: a different disease? Breathe (Sheff) 2016; 12: 43-49.
5) Dartevelle P, Fadel E, Mussot S, Chapelier A, Hervé P, de Perrot M, Cerrina J, Ladurie FL, Lehouerou D, Humbert M, Sitbon O, Simonneau G. Chronic thromboembolic pulmonary hypertension. Eur Respir J 2004; 23: 637-648.
6) Hjalmarsson C, Radegran G, Kylhammar D, Rundqvist B, Multing J, Nisell MD, Kjellström B; SveFPH and SPAHR. Impact of age and comorbidity on risk stratification in idiopathic pulmonary arterial hypertension. Eur Respir J 2018; 51: 1702310.
7) Pugh ME, Sivarajan L, Wang L, Robbins IM, Newman JH, Hemnes AR. Causes of pulmonary hypertension in the elderly. Chest 2014; 146: 159-166.
8) Janssens JP, Pache JC, Nicod LP. Physiological changes in respiratory function associated with ageing. Eur Respir J 1999; 13: 197-205.
9) Örem C. Epidemiology of pulmonary hypertension in the elderly. J Geriatr Cardiol 2017; 14: 11-16.
10) Shimony A, Fox BD, Afilalo J, Rudski LG, Hirsch A, Langleben D. Pulmonary arterial hypertension in the elderly-clinical characteristics and long-term survival. Lung 2012; 190: 645-649.
11) Takahashi Y, Yamamoto K, Tanabe N, Suda R, Koshikawa K, Ikubo Y, Suzuki E, Shoji H, Naito

A, Kasai H, Nishimura R, Sanada TJ, Sugiura T, Shigeta A, Sakao S, Tatsumi K. Characteristics of Japanese elderly patients with pulmonary arterial hypertension. Pulm Circ 2020; 10: 2045894020954158.

12) Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40: 373-383.

13) Huang YQ, Gou R, Diao YS, Yin QH, Fan WX, Liang YP, Chen Y, Wu M, Zang L, Li L, Zang J, Cheng L, Fu P, Liu F. Charlson comorbidity index helps predict the risk of mortality for patients with type 2 diabetic nephropathy. J Zhejiang Univ Sci B 2014; 15: 58-66.

14) Hurdman J, Condliffe R, Elliot CA, Davies C, Hill C, Wild JM, Capener D, Sephton P, Hamilton N, Armstrong IJ, Billings C, Lawrie A, Sabroe I, Akil M, O'Toole L, Kiely DG. ASPIRE registry: assessing the spectrum of pulmonary hypertension identified at a referral centre. Eur Respir J 2012; 39: 945-955.

15) Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaici A, Weitzenblum E, Cordier JF, Chabot F, Dromer C, Pison C, Reynaud-Gaubert M, Haloun A, Laurent M, Hachulla E, Simonneau G. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med 2006; 173: 1023-1030.

16) Hoeper MM, Huscher D, Ghofrani HA, Delcroix M, Distler O, Schweiger C, Grunig E, Staehler G, Rosenkranz S, Halank M, Held M, Grohé C, Lange TJ, Behr J, Klose H, Wilkens H, Filusch A, Germann M, Ewert R, Seyfarth HJ, Olsson KM, Opitz CF, Gaine SP, Vizza CD, Vonk-Noordegraaf A, Kaemmerer H, Gibbs JS, Pittrow D. Elderly patients diagnosed with idiopathic pulmonary arterial hypertension: results from the COMPERA registry. Int J Cardiol 2013; 168: 871-880.

17) Freed DH, Thomson BM, Berman M, Tsui SS, Dunning J, Sheares KK, Pepke-Zaba J, Jenkins DP. Survival after pulmonary endarterectomy: effect of residual pulmonary hypertension. J Thorac Cardiovasc Surg 2011; 141: 383-387.

18) Berman M, Hardman G, Sharples L, Pepke-Zaba J, Sheares K, Tsui S, Dunning J, Jenkins DP. Pulmonary endarterectomy: outcomes in patients aged >70. Eur J Cardiothorac Surg 2012; 41: e154-60.

19) Shapiro BP, McGoon MD, Redfield MM. Unexplained pulmonary hypertension in elderly patients. Chest 2007; 131: 94-100.

20) Foley RJ, Wilcox D, Walsh SJ, Azrin M, Hager WD. Survival of geriatric idiopathic pulmonary arterial hypertension patients. Conn Med 2011; 75: 11-15.

21) Robbins IM, Hemnes AR, Pugh ME, Brittain EL, Zhao DX, Piana RN, Fong PP, Newman JH. High prevalence of occult pulmonary venous hypertension revealed by fluid challenge in pulmonary hypertension. Circ Heart Fail 2014; 7: 116-122.

22) Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, Vasan RS, Levy D. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. Hypertension 2004; 43: 1239-1245.

23) Lador F, Herve P. A practical approach of PH in the elderly. Semin Respir Crit Care Med 2013; 34: 654-664.